Anti-müllerian hormone variability during ovarian stimulation for IVF: A novel approach to predict fertility treatment outcomes

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Anti-Müllerian hormone (AMH) is nowadays one of the most important ovarian reserve markers, useful for individualizing the therapeutic strategy in patients with infertility. In this short review, we have summarized the variability AMH shows during the natural cycle and during ovarian stimulation protocols, looking for the best moment to measure AMH.

Key Words: *Embryo development; Blastocysts; Menstrual cycle; Female gametes; Pregnancy*

Abbreviations: *AMH Anti-müllerian hormone; IVF-ICSI In vitro fertilization-intracytoplasmatic sperm injection; ART Assisted reproductive techniques; FSH Follicle stimulating hormone; HP-HMG Highly purified human menotropin; hCG Human chorionic patients; MII Metaphase II; AFC Antral follicle count*

During the last few years, Anti-Müllerian hormone (AMH) has emerged as one of the most important clinical markers for ovarian reserve in assisted reproductive techniques (ART). It has a strong correlation with the number of follicles, it is operator independent, can predict reproductive lifespan and it is useful as baseline assessment preceding ovarian stimulation for individualizing the therapeutic strategy. Through paracrine mediation, AMH contributes to control follicle development from a reserve of primordial follicles constituted early in life (1) and its production seems to be independent of follicle stimulating hormone (FSH).

AMH has been considered an ovarian reserve marker that can be measured independently of the cycle phase with minimal fluctuations in the menstrual cycle (2). Initially, those fluctuations were associated with the analysis, as analytical variability. However, recent studies have revealed important inter and intra-cycle variations and during ovarian stimulation for ART that cannot be explained only by analytical variability, underlying the presence of a biologic AMH dynamic that is not yet fully understood. Inter-individual differences are dependent on several factors: ethnicity, hormonal contraceptive use, body mass index and smoking (2). Hence, fluctuations in the same woman, intercycle and intracycle during natural cycles question whether a single AMH measurement is enough for decision-making in our daily practice.

THE INTRACYCLE VARIATIONS DURING OVARIAN STIMULATION FOR IVF-ICSI

In women undergoing ovarian stimulation for IVF-ICSI, serum AMH levels decrease gradually during the follicular phase. This dynamic has been demonstrated in normo-responders, but also in patients with low and high ovarian reserve (3-5). These findings are similar when recombinant FSH or HP-HMG is used in both, agonist or antagonist protocols (6). After the hCG administration, the AMH levels continue to decline until the mid-luteal phase and the nadir seems to be approximately after 4 days of the hCG administration. Then, AMH increases and returns to baseline levels two weeks after hCG administration regardless of treatment outcome (pregnancy or not) (5-7).

AMH levels and the rate of AMH decline throughout the stimulation are correlated with IVF-ICSI outcomes as the number of total eggs retrieved, rate of metaphase II and the total number of top quality embryos (8). Moreover, Styer et al. published, as well, an association between AMH, embryo development and clinical pregnancy rates (9).

These results suggest that AMH may somehow be related not only with the quantity but also with the quality of the female gametes and therefore, to embryo quality and pregnancy outcomes. Recent publications demonstrated that age and AMH are independently related with the rates of euploid blastocysts, and there is an increased risk of miscarriage in women with low AMH at any age (10,11).

AMH VARIATIONS OBSERVED DURING THE NATURAL CYCLE

Over the past, we have been considering for a long time that AMH was stable throughout the menstrual cycle 2 (12,13). However, nowadays, several studies have reported conflicting results on its biological variability during the natural cycle of a woman.

Initially, the AMH variations observed during the cycle were considered as analytical variability. It is true that different platforms will deliver different results depending on which molecular form of AMH is being measured, sample storage, freezing of samples, the assay protocols and manual or automated methods used (14). However, huge biological variations have been recently published that cannot be only explained because of the analysis.

During the natural cycle, serum AMH levels seem to be higher during the follicular phase than the luteal phase in women with normal, high and low ovarian reserve (15) and Hadlow et al. (16) described the total average of intraindividual AMH variability in the ovarian cycle was 20% and the biological variation was at least twice the analytical variation. Young women have a pattern of fluctuation intra-cycle that seems to be different in older women (17) and also, very short-term dynamics were described with circadian variation in AMH levels (18). Short-term inter-cycle variations have been reported as well, probably caused by a biological variation in the number of AMH-producing follicles, similarly to the inter-cycle variations showed by the antral follicle count (AFC) or the inter-cycle variations of the ovarian response with same stimulation protocols (19).

THE BEST MOMENT TO MEASURE AMH

Nowadays, it seems clear that AMH can fluctuate during the menstrual cycle with great variations. Not only intra-cycle but also short-term inter-cycle variations that cannot be explained by the AMH-assaying. This variability should be considered carefully, before making any decision in assisted reproductive technologies.

Hence, when should AMH is measured to obtain reliable results? Based on the variations this hormone shows during the whole cycle, it would be useful during our daily work to standardize the moment for the analysis, as the results for our patients will be more homogeneous. As a routine, we perform the AFC during the first days of the cycle, before starting the ovarian stimulation, so we visualize by ultrasound the follicles that would be expected to respond to the medication. However, a complete evaluation including both ovarian markers, AMH and AFC during the early follicular phase, will provide accurate information about the ovarian reserve, the prognosis of

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the ovarian stimulation and will be helpful to decide a tailored dosage of medication for each patient. The balance between activating and opposing factors at the start of each cycle will produce a different number of follicles available for the stimulation every month, and that would be an appropriate moment for AMH to predict ovarian response more accurately. In recent publications, basal AMH levels on days 1-3 of cycle show a good correlation with the number of oocytes retrieved, number of metaphase II (MII) and number of fertilized oocytes (4,8). It is clear than further investigations evaluating the dynamics for AMH and its correlations with treatment outcomes should be developed but, as a routine in our daily practice, to measure AMH during the early follicular phase and to correlate the results with the antral follicle count would be useful in order to provide adequate information and accurate results for the ovarian stimulation during the IVF-ICSI treatments.

CONCLUSION

Anti-Müllerian Hormone is an important marker for ovarian reserve and egg quality, but shows important variability during the natural cycle and during ovarian stimulation for IVF-ICSI treatments. To standardize the analysis during the first days of the cycle will provide homogeneous measurements and more accurate information to individualize our advice for couples undergoing fertility treatments.

REFERENCES

1. Monniaux D, Clément F, Dalbiés Tran R, et al. The ovarian reserve of primordial follicles and the dynamic reserve of antral growing follicles: What is the link? Biol Reprod. 2014;90:1-11.
2. La Marca A, Grisendi V, Griesinger G. How much does AMH really vary in normal women? Int J Endocrinol 2013;2013:959487.
3. Melado L, Fernández-Nistal A, Martínez V, et al. Anti-müllerian hormone dynamics during GNRH-antagonist short protocol for IVF/ICSI in women with varying ovarian reserve levels. Minerva Ginecol. 2017;69(2):128-34.
4. Lee JR, Kim SH, Kim SM, et al. Anti-müllerian hormone dynamics during controlled ovarian hyper stimulations and optimal timing of measurement for outcome prediction. Hum Reprod. 2010;25:2597-604.
5. Weintraub A, Margalioth EJ, Chetrit AB, et al. The dynamics of serum anti-müllerian hormone levels during controlled ovarian hyper stimulation with GnRH-antagonist short protocol in polycystic ovary syndrome and low responders. Eur J Obstet Gynecol Reprod Biol. 2014;176:163-7.
6. Fanchin R, Schonauer LM, Righini C, et al. Serum anti-müllerian hormone dynamics during controlled ovarian hyperstimulation. Hum Reprod. 2003;18:328-33.
7. Fanchin R, Méndez Lozano DH, Louafi N, et al. Dynamics of serum anti-müllerian hormone levels during the luteal phase of controlled ovarian hyper stimulation. Hum Reprod. 2005;20(3):747-51.
8. Melado Vidales L, Fernández-Nistal A, Martínez Fernández V, et al. Anti-müllerian hormone levels to predict oocyte maturity and embryo quality during controlled ovarian hyper stimulation. Minerva Ginecol. 2017;69(3):225-32.
9. Styer AK, Gaskins AJ, Brady PC, et al. Dynamic anti-müllerian hormone levels during controlled ovarian hyper stimulation predict in vitro fertilization response and pregnancy outcomes. Fertil Steril. 2015;104(5):1153-61.
10. La Marca A, Minasi MG, Sighinolfi G, et al. Female age, serum anti-müllerian hormone level, and number of oocytes affect the rate and number of euploid blastocysts in *in vitro* fertilization/intracytoplasmic sperm injection cycles. Fertil Steril. 2017;108(5):777-83.
11. Tarasconi B, Tadros T, Ayoubi JM, et al. Serum anti-müllerian hormone levels are independently related to miscarriage rates after *in vitro* fertilization-embryo transfer. Fertil Steril. 2017;108(3):518-52.
12. Hehenkamp WJ, Looman CW, Themmen AP, et al. Anti-mullerian hormone levels in the spontaneous menstrual cycle does not show substantial uctuation. J Clin Endocrinol Metab. 2006;91:4057-63.
13. La Marca A, Giulini S, Tirelli A, et al. Anti-mullerian hormone measurement on any day of the menstrual cycle strongly predicts ovarian response in assisted reproductive technology. Hum Reprod. 2007;22:766-71.
14. Rustamov O, Smith A, Roberts SA, et al. The measurement of anti-müllerian hormone: a critical appraisal. J Clin Endocrinol Metab. 2014;99(3):723-32.
15. Gorkem U, Kucukler FK, Togrul C, et al. Anti-müllerian hormone exhibits a great variation in infertile women with different ovarian reserve patterns. Aust N Z J Obstet Gynaecol. 2017.
16. Hadlow N, Brown SJ, Habib A, et al. Quantifying the intraindividual variation of anti-müllerian hormone in the ovarian cycle. Fertil Steril. 2016;106(5):1230-7.
17. Overbeek A, Broekmans FJ, Hehenkamp WJ. Intra-cycle fluctuations of anti-müllerian hormone in normal women with regular cycle: A re-analysis. Reprod Biomed Online. 2012;24:664-9.
18. Bungum L, Jacobsson AK, Rosén F, Becker C, et al. Circadian variation in concentration of anti-müllerian hormone in regularly menstruating females: relation to age, gonadotrophin and sex steroid levels. Hum Reprod. 2011:26(3):678-84.
19. Rombauts L, Lambalk CB, Schultze-Mosgau A, et al. Intercycle variability of the ovarian response in patients undergoing repeated stimulation with corifollitropin alfa in a gonadotropin-releasing hormone antagonist protocol. Fertil Steril. 2015;104(4):884-90.